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## APPLICATION FOR UNITED STATES PATENT

### HIGH PRESSURE PARALLEL REACTOR

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# HIGH PRESSURE PARALLEL REACTOR

## FIELD OF THE INVENTION

The present invention relates generally to parallel batch reactors, and more particularly, to high pressure reactors for parallel synthesis and screening of materials.

## BACKGROUND OF THE INVENTION

The discovery of new materials with novel chemical and physical properties often leads to the development of new and useful technologies. The discovery of new materials depends largely on the ability to synthesize and analyze new compounds. Scientists are thus, always searching for a more efficient, economical, and systematic approach for the synthesis of novel materials. Combinatorial technologies are often used to accelerate the speed of research, maximize the opportunity for breakthroughs, and expand the amount of available information. Combinatorial chemistry involves synthesizing microscale quantities of a compound and then testing thousands of compounds quickly.

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The use of combinatorial technologies allows high density libraries of very large numbers of materials to be created using parallel synthesis. High throughput screens are then used to test these materials for desired properties to identify potential optimized compounds. Combinatorial technologies may be used to optimize and validate many variations of a material, formulation, or microdevice. Variables such as temperature, pressure, atmosphere, and concentration can be quickly adjusted and tested in a single experiment.

In parallel synthesis, different compounds are synthesized in separate vessels, often in an automated fashion. A commonly used format for parallel synthesis is a multi-well microtiter plate. Robotic instrumentation can be used to add different reagents or catalysts to individual wells of a microtiter plate in a predefined manner to produce combinatorial libraries. Devices have been developed for automating combinatorial parallel synthesis. One such device includes reaction blocks containing multiple reaction vessels each individually sealed. These devices often require substantial sealing arrangements and do not provide means for pressurizing the individual vessels. Other devices supply an inert gas to a plurality of reactor vessels, however, the gas is only supplied at one or two psi above atmospheric pressure to control the environment during the reaction. These devices are not designed to withstand high pressure operation.

## SUMMARY OF THE INVENTION

An apparatus and method for synthesis and screening of materials are disclosed.

5 In one embodiment, an apparatus of the present invention comprises a base having a plurality of reaction wells, each of the reaction wells having a closed lower end and open upper end for receiving reactant materials. A cover is configured for sealing engagement with the base to form a housing enclosing the plurality of reaction wells and defining a common pressure chamber in communication with the reaction wells. The apparatus further includes an inlet  
10 port in communication with the pressure chamber for supplying pressurized fluid to the chamber to pressurize the reaction wells. The housing is configured to sustain a pressure substantially above atmospheric pressure.

The apparatus may be configured to have external base dimensions generally corresponding to standard microtiter plate dimensions for use with  
15 automation equipment designed for use with microtiter plates. The apparatus may include 96 reaction wells arranged in an 8 by 12 array or 12 reaction wells arranged in a 3 by 4 array, for example.

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A flow restriction device having a plurality of vent holes may be positioned adjacent to open ends of the reaction wells with the vent holes in alignment with the reaction wells to provide communication between the reaction wells and the pressure chamber while reducing cross-talk between the reaction wells. The flow restriction device may also include a plurality of check valves or micromachined orifices, for example.

In another aspect of the invention, the apparatus comprises a pressure chamber sized for receiving a microtiter plate comprising a plurality of reaction wells for receiving components of the synthesis or screening. Each of the reaction wells has a closed lower end and an open end exposed to the pressure chamber. The apparatus further includes a cover moveable between an open position for receiving the microtiter plate and a closed position for creating a sealed pressure chamber. An inlet port is formed within the apparatus in communication with the pressure chamber for supplying fluid pressurized substantially above atmospheric pressure to the pressure chamber to simultaneously pressurize each of the reaction wells from an external pressure source. The apparatus also includes a quick-operating fastening device operable to position the cover in its closed position and hold the cover in sealing engagement with the pressure chamber.

A method for reacting a plurality of materials in parallel with a reactor vessel having a plurality of reaction wells formed in a base of the vessel, each of

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the reaction wells having an open end exposed to a common pressure chamber defined by the reactor vessel, generally comprises: opening a cover of the reactor vessel; inserting components into the reaction wells; closing the cover of the reactor vessel to create a sealed chamber; and supplying a gas substantially above  
5 atmospheric pressure that reacts with the components within the reaction wells.

In another aspect of the present invention, an apparatus for use in parallel reaction of materials comprises a base having a plurality of reaction wells and a cover configured for sealing engagement with the base to form a housing enclosing the plurality of reaction wells and defining a common pressure chamber  
10 in communication with the plurality of reaction wells. Each of the reaction wells has a closed lower end and an open upper end for receiving components of the reaction. The apparatus further includes a flow restriction device positioned adjacent to the open ends of the reaction wells to provide communication between the reaction wells and the pressure chamber while reducing cross-talk between the  
15 reaction wells. An inlet portion is formed in the apparatus for supplying pressurized fluid to the pressure chamber to pressurize the plurality of reaction wells.

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The above is a brief description of some deficiencies in the prior art and advantages of the present invention. Other features, advantages, and embodiments of the invention will be apparent to those skilled in the art from the following description, drawings, and claims.

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### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a an exploded view of a reactor vessel of the present invention.

Fig. 2 is a perspective of the reactor vessel of Fig. 1.

Fig. 3 is a plan view of the reactor vessel of Fig. 1

Fig. 4 is a side view of the reactor vessel of Fig. 1.

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Fig. 5 is a front view of the reactor vessel of Fig. 1.

Fig. 6 is a plan view of the reactor vessel of Fig. 1 with internal parts of the vessel shown in phantom.

Fig. 7 is a cross-sectional view of the vessel taken in the plane including line 7--7 of Fig. 6.

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Fig. 8 is a cross-sectional view of the vessel taken in the plane including line 8--8 of Fig. 6.

Fig. 9 is a cross-sectional view of the vessel taken in the plane including line 8--8 of Fig. 6 with coil springs disposed at a closed bottom of reaction wells to force vials within the wells upward against a cover plate.

5 Fig. 10 is a flowchart illustrating a process utilizing the reactor vessel of Fig. 1.

Fig. 11 is a perspective of a second embodiment of a reactor vessel of the present invention.

Fig. 12 is a perspective of the reactor vessel of Fig. 11 in an open position.

Fig. 13 is a cross-sectional view of the reactor vessel of Fig. 11.

10 Corresponding reference characters indicate corresponding parts throughout the several views of the drawings.



## DETAILED DESCRIPTION OF THE INVENTION

5 The following description is presented to enable one of ordinary skill in the art to make and use the invention. Descriptions of specific embodiments and applications are provided only as examples and various modifications will be readily apparent to those skilled in the art. The general principles described herein may be applied to other embodiments and applications without departing from the scope of the invention. Thus, the present invention is not to be limited to the embodiments shown, but is to be accorded the widest scope consistent with the principles and features described herein. For purpose of clarity, details relating to technical material that is known in the technical fields related to the invention have not been described in detail.

10 Referring now to the drawings, and first to Figs. 1-6, an apparatus of the present invention is shown and generally indicated at 20. The apparatus 20 comprises a reactor vessel defining a pressure chamber 26 and a plurality of reaction wells 30 internal to the reactor vessel and exposed to the pressure chamber. The pressure chamber 26 is pressurized with an inert gas to pressurize components within the reaction wells or a gas selected to react with components within the reaction wells. The common pressurization area defined by the pressure chamber 26 simplifies the sealing required as compared to individually sealed reaction wells of conventional devices. Furthermore, the common pressure

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chamber 26 exposes each reaction well 30 to generally the same pressure, whereas individually pressurized reaction wells are often exposed to varying pressures due to leaks or uneven filling (when heated), which introduces undesirable variability into the testing.

5           The apparatus 20 may be used to perform parallel synthesis or screening of materials or other experimentation involving reactions of multiple components. For example, the apparatus 20 may be utilized for reactions where one or more components is a gas such as hydrogenations, carbonilations, oxidations and polymerizations with gaseous monomers. The apparatus may also be used with  
10           homogeneous, chiral, or heterogeneous catalysts (i.e., catalysts which enable catalytic reactions to occur with the reactants and catalysts residing in different phases (e.g., solid/liquid, solid/gas, liquid/gas)), or polyolefin and butyl rubber polymerizations. It is to be understood that the applications described herein are merely examples of uses of the apparatus 20 and methods of the present invention  
15           and that the apparatus may be used for other applications without departing from the scope of the invention.

As shown in Figs. 1-3, the reactor vessel has an overall rectangular shape and comprises two sections; a base member 32 and a top member (or cover) 34 (Figs. 1 and 2). The combination of the base 32 and cover 34 form a manifold  
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32 and cover 34 define an internal cavity which forms the pressure chamber 26 (Figs. 7 and 8). The pressure chamber may have a volume of approximately ten cubic inches, for example. The base member 32 includes a bottom 40, a pair of opposing side walls 42, and a pair of opposing end walls 44 (Figs. 4 and 5). The cover 34 includes a periphery flange 48 configured to mate with a periphery flange 50 extending from the walls 42, 44 of the base member 32 (Figs. 1 and 2). The flanges 48, 50 of the cover 34 and base 32 include a plurality of openings 52 (ten shown) for receiving bolts 54, screws, or other fasteners. The base 32 and cover 34 may also be attached by other suitable attachment means such as external clamps. The base 32 includes a groove 58 extending around a periphery thereof for receiving a sealing gasket 60 (Figs. 1, 7 and 8). The gasket 60 is interposed between the base 32 and cover 34 to provide a seal therebetween. The groove 58 for the gasket 60 may be machined into either a bottom surface of flange 48 of the cover 34, or a top surface of flange 50 of the base 32. The gasket 60 may be an o-ring formed from PTFE, neoprene, butyl rubber, Teflon coated elastomer, Viton, expanded Teflon, graphite, or Kalrez, for example.

The reactor vessel includes an inlet port 70 in fluid communication with the pressure chamber 26 (Figs. 2 and 6). A quick release fitting 72 is preferably coupled to the inlet port 70 for attaching the port to a flexible hose or rigid tube (not shown) connected to a pressure supply device. The flexible hose or rigid gas supply tube may also be left connected and the fill valve open during an

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experiment. If a vacuum is to be applied to the chamber 26, a vacuum supply device may also be attached to the pressure port 70 or another inlet port on the reactor vessel. A fill valve 74 is attached to the inlet port to control the application of pressure to the vessel. The fill valve 74 may have a manual or electronic pressure control valve. A pressure sensor (not shown) may be inserted inline with the fill valve 74 or inserted into the pressure chamber 26 or one or more of the reaction wells 30 to monitor the pressure within the vessel. The inlet supply system may allow for a series of purging, venting, or pressurization cycles, with one or more gases or with vacuum without disconnecting the supply lines. The pressure source may be an inert gas such as nitrogen, argon, helium, carbon dioxide, or air, or a reactive gas such as hydrogen, oxygen, hydrogen chloride, or ammonia. Mixtures of gases may also be used. The reactor vessel further includes an opening for a pressure release valve 78 to prevent over pressurization of the vessel.

The base 32 and cover 34 may be formed from aluminum, titanium, steel, or any other suitable material. The material of the reactor vessel is preferably selected to be chemically inert to the reaction of interest and allow the vessel to operate at high temperature (e.g., 150-250° C) and high pressure (10-1000 psig). For example, if the apparatus is to be operated at 290 psig and 150° C (for e.g., gaseous monomer or reagent use), 6061-T6 aluminum, which has been hard anodized, may be used. If the operating pressure is 1000 psig and operating

temperature is 200° C, the material may be 17-4PH, H1100 stainless steel or 6Al-4V titanium. For some applications, the stainless steel or other material may be coated or surface treated. It is to be understood that the temperature or pressure applied to the reactor vessel or the materials used to form the base 32 and cover 34 may be different than described herein without departing from the scope of the invention. The reactor vessel is preferably designed to withstand pressures substantially above atmospheric pressure (i.e., 14.7 psi). The vessel is preferably designed to withstand pressures above 10 psig, and more preferably pressures above 50 psig. The vessel may also be designed, for example, to operate at pressures of 15 psig, 20 psig, 30 psig, 40 psig, 100 psig, 300 psig, 500 psig, 1000 psig, or other selected pressures. The vessel is preferably designed to withstand temperatures up to 200° C, but may also be designed to operate at 250° C, 315° C, or higher temperatures.

The reaction wells 30 are preferably integrally formed within the base member 32 or another member coupled to the base member. As shown in Figs. 7 and 8, the wells 30 are machined into an upper planar surface 80 of the base member 32. The wells 30 are preferably machined as close as possible to one another. Similarly, a bottom surface 84 of the well 30 is left with sufficient material to withstand pressures applied to the wells. The base member 32 may also serve as a temperature control means for controlling the reaction temperature in the reaction wells 30, in which case the bottom surface 84 of the reaction wells

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30 is sized to provide the required conductivity between an external heat source, such as a heating plate on which the reaction vessel is placed, and the reaction wells. The reactor vessel may be placed, for example, on a temperature control plate which is contiguous to the lower surface of the reactor vessel for the transfer of thermal energy therebetween. The thermal control plate may be a plate formed of thermally conductive material with passages for conveying a heating or cooling fluid through the plate, or other heat generating device, as is well known by those skilled in the art. If the reactor vessel is designed for heating components within the reaction wells, the manifold is preferably formed from a thermally conductive material, such as an aluminum alloy. The reactor vessel may also be placed in an oven to heat the components within the reaction wells 30.

The reaction wells 30 may also be formed within a block separate from the base of the reactor vessel. For example, the reaction wells may be formed within a metal, nylon, Teflon, or other polymer material block. The block may be a microtiter plate, as described below.

The reaction vessel is preferably configured to correspond to a standard microtiter plate format. The microtiter plate is a widely used means for handling, processing, and analyzing large numbers of small samples in the biochemistry and biotechnology fields. Typically, a microtiter plate is approximately 3.4 inches wide and 5.0 inches long and contains 96 identical sample wells in an 8 by 12

rectangular array on 9 millimeter centers. A wide variety of equipment is available for automatic handling, processing, and analyzing of samples in this microtiter plate format. It is to be understood that depending upon the scale of the apparatus, the block may contain a greater or fewer number of reaction wells of various geometries arranged in any configuration.

In the embodiment shown in Figs. 1-8, the base includes 96 reaction wells 30 in an 8 by 12 array, corresponding to the standard microtiter plate format used in industry for high throughput screening of compounds and biological assays. In preferred embodiments, the number of test wells is equal to  $96 \times N$ , where  $N$  is an integer ranging from 1–100, preferably 1–10, and more preferably 1–5. The outside dimensions of the vessel preferably correspond to the standard microtiter format (e.g., approximately 5.0 inches long ( $l$ ), 3.4 inches wide ( $w$ ), and 0.5 – 2.0 inches high ( $h$ )) (Figs. 4 and 5). For example, the reactor vessel may have a length ( $l$ ) of 5.030 inches, a width ( $w$ ) of 3.365 inches and height ( $h$ ) of 2.175 inches. It is to be understood that the reactor vessel may have external dimensions different than the standard microtiter plate format or have a different number or arrangement of reaction wells 30 without departing from the scope of the invention. For example, the reactor may have a 3 by 4 array of reaction wells, each well having a fluid volume of approximately 16 milliliters. Other arrays, such as a 3 by 5 array or a 100 by 100 array may also be used.

Components used in the synthesis or screening may be added directly to the reaction wells 30 or the reaction wells 30 may be lined with an inert liner to prevent reactions between chemicals and the base member. As shown in Figs. 7 and 8, vials 90 may be inserted into the wells 30 for receiving the components.

5 The vials 90 may be formed from glass or other suitable materials. The vials 90 preferably extend above the reaction well openings formed in the base member 32. The glass vials 90 may have an internal volume of approximately 2 milliliters, for example.

10 A flow restriction device 92 is preferably placed over the reaction wells 30 to reduce vapor phase cross-talk between adjacent wells 30 (Figs. 7 and 8). The flow restriction device 92 may comprise, for example, a cover member having a plurality of very small vent holes 96 aligned with the reaction wells 30 to provide fluid communication between the wells and the pressure chamber 26. The cover member 92 may be a rigid metal plate with vent holes drilled therein or a flexible elastomeric sheet (e.g., septum sheet) with vent holes punched therein. The member 92 may also be a porous sheet with the pores providing fluid communication between the reaction wells 30 and the pressure chamber 26. The flow restriction device 92 may also include check valves which allow flow into the reaction wells 30 but restrict flow from the reaction wells to the pressure chamber 26. The vent holes within the flow restriction device 92 may also be micromachined flow restrictions.

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A coil spring 95 (or elastomeric material) may be placed at the bottom of each of the reaction wells to force the vials upward and bias the open ends of the vials against the flow restriction device 92, as shown in Fig. 9. The flow restriction device 92 is preferably removably attached to the base member with bolts 98 or other suitable attachment means. The flow restriction device 92 may also be coupled or integrally formed with the cover 34 so that the device is automatically disposed adjacent to the open ends of the reaction wells 30 when the cover is mated with the base member 32 and closed.

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The materials of the base member 32, cover 34, flow restriction device 92, gasket 60, and vials 90 are preferably selected to be chemically suitable for the application (i.e., will not be attacked, solubilized, softened, or otherwise interact with the reagents, solvents, solids, products, or other components which are either added to the vessel or produced during a reaction sequence). The materials are also preferably chosen to assure that reactant, products, or by-products of the reaction are not adsorbed or otherwise trapped by the materials.

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Fig. 10 is a flowchart illustrating a process for utilizing the apparatus 20 of the present invention. At step 100, the cover 34 is removed from the base member 32 (or placed in an open position) to allow access to the interior of the reactor vessel (Figs. 1 and 10). If the reaction wells are not formed in the base member, the block containing the reaction wells is positioned within the base

member 32. The components to be tested are then placed within the reaction wells 30 (step 102). Preferably, the composition of the materials placed within each of the wells 30 varies from one reaction well to the next. The cover plate 92 is then placed over the base member 32 with fastener openings within the plate aligned with openings formed in the base (or reaction well block) (step 104). Bolts 98 or other suitable fasteners, are inserted into the aligned openings to attach the cover plate 92 to the base member 32. The cover 34 is then attached to the base 32 with bolts 54 or other fasteners (step 106). A supply line (not shown) is connected to the quick release coupling 72 at the inlet port 70 and the fill valve 74 is opened until the required pressure is reached within the pressure chamber 26 (step 108) (Figs. 6 and 10). The gas supplied to the vessel may be an inert gas or a gas that reacts with the components placed into the reaction wells 30.

After the pressurized gas is added to the vessel and the pressure chamber 26 has reached the appropriate operating pressure, the fill valve 74 is closed, the supply line is removed, and the entire assembly is inserted into an oven or placed on a heating plate (steps 110 and 112). Agitation of components within the reaction wells 30 may be achieved by shaking or magnetic stirring. For example, the apparatus may be placed on an oven/shaker assembly or a magnetic stirrer may be used to mix the reactants. The base 32 and cover 34 are preferably aluminum or titanium if magnetic stirring is used. Once the reaction is complete, pressure is removed from the pressure chamber 26 through the fill valve 74 or an

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outlet or vent within the housing (step 116). The cover 34 is opened and the cover plate 92 is removed from the base member 32 (step 118). If vials 90 are used, the vials are removed from the reaction wells 30 for analysis or their contents are sampled (step 120). If the materials are placed directly into the reaction wells 30, a pipette or other suitable tool may be used to remove contents of the wells. The contents of the reaction wells 30 are then analyzed by techniques well known by those skilled in the art.

Figs. 11-13 show a second embodiment of a reactor vessel of the present invention, generally indicated at 200. The reactor vessel 200 includes a pressure chamber 202 sized for receiving a microtiter plate 205. The pressure chamber 202 may be formed from 6061-T6 aluminum, or any other suitable material. The vessel 200 includes a fill valve 208 and pressure relief valve 210 in communication with the pressure chamber 202. The vessel 200 further includes a door 204 movable between an open position (shown in Fig. 12) for inserting the microtiter plate 205 and a closed position (shown in Fig. 11) for creating a sealed pressure chamber. A quick-operating fastening device is used to move the door 204 to its closed position and sealingly engage the door with the pressure chamber 202. The door 204 may be formed from stainless steel or other suitable materials. The door 204 includes two pin receiving openings 211 formed in a top surface of the door and extending longitudinally through a portion of the door (Fig. 12). The openings 211 are sized for receiving door latching pins 212 which extend



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The entire assembly 200 may be placed into an oven or on an orbital shaker. As shown and described above, the vessel 200 is compact since it is sized specifically for receiving a microtiter plate. For example, the vessel 200 may have a length (L) of 7.625 inches. It is to be understood that the vessel may have different configurations than shown and described herein without departing from the scope of the invention. For example, the vessel 200 may be sized for receiving more than one microtiter plate or have a quick release mechanism different than shown.

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The following examples illustrate principles and advantages of the invention.

Example 1: Heterogeneous Catalysis

The reaction vessel used for this experiment was formed from 6061-T6 aluminum and had 96 reaction wells. The following components were first added to a 4 ml glass vial to form a solution:

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10.9 mg of 1% palladium on activated carbon;

3.090 ml ethyl alcohol; and

0.020 ml nitrobenzene.

The vial was shaken by hand and then placed on a stir plate to mix using a magnetic micro-stir bar within the vial. Samples containing 0.377 ml of the

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solution were pipetted into two of the 96 wells. The reactor was then sealed with an o-ring and the cover was placed over the base of the reactor. Bolts were inserted into the aligned openings of the base and cover and each torqued to 10 ft-lbs. A gas supply line was attached to the reactor vessel and the vessel was

5 pressurized and vented three times to remove the air inside. The vessel was then pressurized to 30 psig with pure hydrogen gas. The fill valve was closed and the gas line disconnected before placing the apparatus in a mixing oven. The reactor was heated at 30°C for one hour while mixing. The vessel was then vented and opened. Thin layer chromatography (TLC) and high pressure liquid

10 chromatography (HPLC) were performed and showed that the nitrobenzene in both wells was fully converted and only the desired product, aniline, was detected.

#### Example 2: Cross-Talk

In the following example, two aluminum reactor vessels each having 96

15 reaction wells were used. One of the reactor vessels included a septum sheet (flow restriction device) having punctured holes aligned with each of the reaction wells. The other reactor vessel did not include a flow restriction device to reduce cross talk between reaction wells. Blanks of pure toluene were placed in eight

20 reaction wells within each of the reactors. The remaining reaction wells contained a mixture of heptane, toluene, and octene. Nitrogen gas was supplied to

each of the reactor vessels at an initial pressure of 160 psig and temperature of 25°C. The final pressure within the vessels was 260 psig after 45 minutes in an oven at 200°C. The following are the gas chromatography (GC) test results:

The original mix before the test included the following components:

5                    43.47% heptane, 49.03% toluene, and 7.50% octene.

The original toluene blank before the test contained:

0.05% (in heptane position), 99.93% toluene, and 0.02% (in octene position).

The average composition of the mix (with flow restriction device) after the test was:

41.51% heptane, 51.35% toluene, and 7.14% octene.

The average composition of the mix (without flow restriction device) after the test was:

41.82% heptane, 50.50% toluene, and 7.68% octene.

15                    Thus, some vapor was being transported out of the reaction wells in both reactor vessels.

The average composition of the toluene blanks (with flow restriction device) after the test was:

0.47% heptane, 99.49% toluene, and 0.04% octene.

The average composition of the toluene blanks (without flow restriction device) after the test was:

17.11% heptane, 81.26% toluene, and 1.68% octene.

5 Thus, the flow restriction device helped to prevent vapor transport (cross-talk) into the wells.

As can be observed from the foregoing, the apparatus 20, 200 and method of the present invention have numerous advantages. The reaction wells 30 are all exposed to a common pressure chamber 26 which results in simplification of the apparatus, reduced variation between pressurization of the reaction wells, and reduced manufacturing and processing costs. The apparatus is well suited for auxiliary processes including heating, shaking, and robotic automation. Furthermore, since there is a fewer number of sealed volumes (e.g., one versus ninety-six) the apparatus provides increased reliability and easier maintenance. The design of the reactor vessel allows for pressurization of the reaction wells with a pressurized gas at a pressure substantially above atmospheric pressure.

Although the present invention has been described in accordance with the embodiments shown, one of ordinary skill in the art will readily recognize that there could be variations made to the embodiments without departing from the scope of the present invention. Accordingly, it is intended that all matter



contained in the above description and shown in the accompanying drawings shall  
be interpreted as illustrative and not in a limiting sense.

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